RESEARCH ARTICLE

Systemic Analysis on Risk Factors for Breast Cancer Related Lymphedema

Ya-Qun Zhu, Yu-Huan Xie, Feng-Huan Liu, Qi Guo, Pei-Pei Shen, Ye Tian*

Abstract

<u>Background</u>: To evaluate risk factors for upper extremity lymphedema due to breast cancer surgery. <u>Materials and Methods</u>: Clinical studies published on PubMed, Ovid, EMbase, and Cochrane Library from January 1996 to December 2012 were selected. <u>Results</u>: Twenty-five studies were identified, including 12,104 patients. Six risk factors related to the incidence of lymphedema after breast cancer treatment were detected: axillary lymph node dissection (OR=3.73, 95%CI 1.16 to 11.96), postoperative complications (OR=2.64, 95%CI 1.10 to 6.30), hypertension (OR=1.83, 95%CI 1.38 to 2.42), high body mass index (OR=1.80, 95%CI 1.30 to 2.49), chemotherapy (OR=1.38, 95%CI 1.07 to 1.79) and radiotherapy (OR=1.35, 95%CI 1.10 to 1.66). We found significant protective factors for lymphedema: pathologic T classification (OR=0.57, 95%CI 0.36 to 0.91) and stage (OR=0.60, 95%CI 0.39 to 0.93), while some factors, like age, number of positive lymph nodes, number of lymph node dissection, demonstrated no obvious correlation. <u>Conclusions</u>: Axillary lymph node dissection, postoperative complications, hypertension, body mass index, chemotherapy, radiotherapy are risk factors for lymphedema after breast cancer treatment. Attention should be paid to patients with risk factors to prevent the occurrence of lymphedema.

Keywords: Breast cancer - upper extremity surgery - lymphedema - risk factors

Introduction

Breast cancer related lymphedema (BCRL)is a chronic and common complication caused by abnormal accumulation of protein-rich fluid in the interstitial space secondary to inadequate lymphatic drainage, which manifests unilateral or bilateral upper extremity swelling in the clinical. (Cheville et al., 2003). Lymphedema and its related symptoms (pain, heaviness, tightness, and decreased range of motion) seriously affect recreational and social relationships (Hayes et al.,2012). Patients with BCRL have a lower quality of life, a higher level of anxiety or depression (Pyszel et al., 2006; Heiney et al., 2007).

Due to differences in study designs, measurement methods and criterias , length of follow-up, lymphedema definitions and timing of lymphedema measurement since diagnosis and treatment, previous studies have shown about 20% of breast cancer survivors will develop lymphedema. (sakorafas et al., 2006) In recent years, many studies have established risk factors of BCRL, but conclusions are not consistent, which even contradict each other from some studies. The study systematically reviews the risk factors for BCRL with meta-analysis method to increase the credibility of the conclusions for the purpose of providing scientific evidence for early prevention of lymphedema in clinical work.
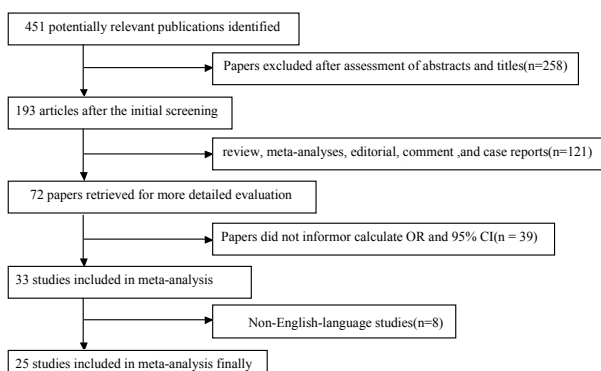
Materials and Methods

Literature Search

We searched comprehensively clinical studies which were published in PubMed, Ovid, EMbase, the Cochrane Library from January 1, 1996 to December 30, 2012. The MeSH headings and keywords in this search used included "breast cancer", "upper extremity", "lymphedema" and "risk factors" Relevant articles were identified and their references were checked for additional studies.The search strategy used: (("Breast Neoplasms" (Mesh) AND "Upper Extremity" (Mesh)) AND ("Lymphedema" (Mesh) OR "Edema" (Mesh)) AND ("1996/01/01" (PDAT) : "2012/12/31" (PDAT))
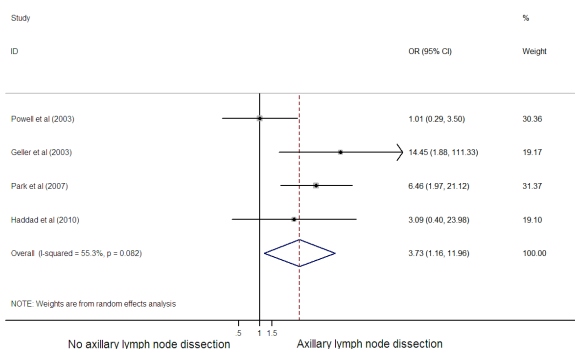
Inclusion and Exclusion Criteria

<u>Inclusion criteria</u>: studies of female patients with unilateral breast cancer; the primary studies of risk factors for BCRL published abroad.

<u>Exclusion criteria</u>: studies of patients with bilateral breast cancer, primary lymphoedema, or metastatic disease (n=258); review, meta-analyses, editorial, comment , and case reports (n=121); studies that did not either inform OR and 95%CI or provide adequate information to calculate the OR and its variance (n=39); non-English-language studies (n=8).

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Figure 1. Flow Diagram of Study Assessment and Inclusion in the Meta-Analysis

**Figure 2. Forest Plot of Axillary Lymph Node Dissection**

Quality evaluation

Two authors assessed the quality of the included studies independently with NOS (Neweastle. Ottawa Scale) iterns by Egger et al. (6) Evaluation indicators include selection , comparability and outcome in cohort study. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Quality of study is divided into A (eight and more stars) and B (seven stars).

Data Abstraction

Two authors selected articles independently with disagreements resolved through discussion with a third author to attain consensus according to predetermined inclusion and exclusion criteria. They extracted data for author, year, study location (country), sample size, method of lymphedema measurement, definition of lymphedema, incidence or prevalence of lymphedema, and risk factors. Lymphedema measurement refers to the technique used to determine the presence of lymphedema and included: arm circumference (centimeters), water displacement (volume), multiple-frequency bioelectrical impedance analysis (MFBIA), clinician diagnosis, self-report and unclear.

Statistical analysis

Establish a database using Excel 2007 software and run preliminary calculation Statistical analysis was done by Stata 10.0 and RevMan 5.2 software. (Cheville et al., 2003) Test heterogeneity of studies using Q test: $p < 0.05$ was considered statistically heterogeneity. Choose a fixed
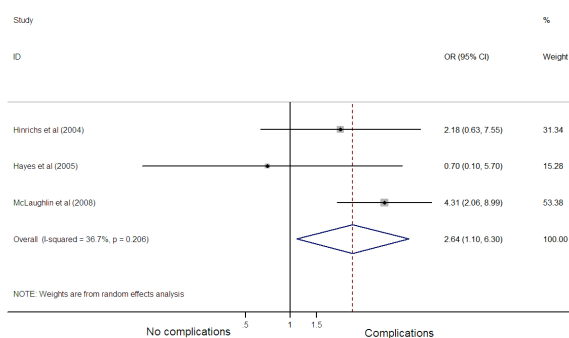
Figure 3. Forest Plot of Postoperative Complications
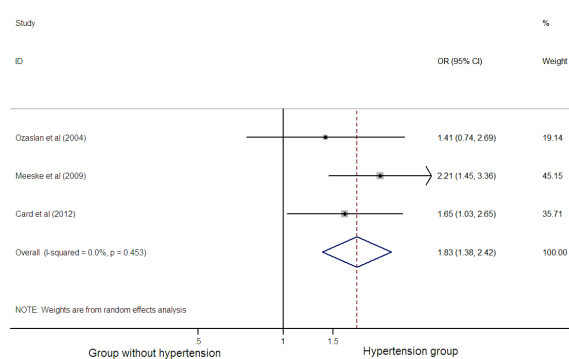
Figure 4. Forest Plot of Hypertension

or random effects model to estimate the pooled OR and 95%CI for these dichotomous factors according to the test results of heterogeneity. If there was heterogeneity between studies, we will use a random effect model (DerSimonian. Laird). If no, use a fixed effect model (Mantel. Haenszel). Subgroup analysis investigate sources of heterogeneity when necessary. (Hayes et al., 2012) Measure the degree of heterogeneity between studies using I-squared test. We can accept heterogeneity when $I^2 \leq 50\%$ in the Cochrane systematic review. Assess the existence of publication bias using Egger's test (Egger et al., 1997).

Results

We identified 451 potentially relevant citations, but 25papers (8-32) were included in our analysis after a series of assessment (Figure 1). 12 studies were from America, 4 studies were from Australia and others from Germany, Italy, Korea, India and so on. Nearly half of studies measured lymphedema based on differences in arm circumference.

Of the 25 studies, 18 studies were eight stars (A) and 7 studies were seven stars (B). The quality of included studies was higher. General characteristics of studies included and study quality in the meta-analysis were as followings: (Table 1). We assessed the presence of publication bias using Egger's test. Nineteen were not statistically significant in publication bias ($p>0.05$) from 21 relevant risks (Table2). The publication bias of this study is small, so the combined results of the research were reliable basically.

In view of inconsistency between t the incidences and risk factors of BCRL among studies, that is there was heterogeneity between studies, we use a random effects model to estimate and analyze various risk factors .We stratified data by different measurement methods and

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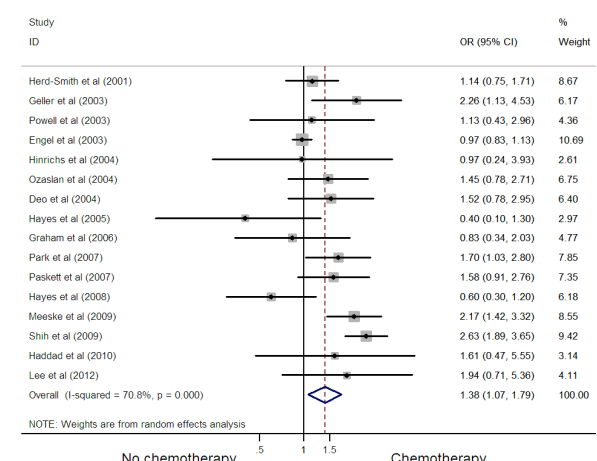**Table 1. General Characteristics of Studies Included in the Meta-analysis**

Author	Year	Study location	Sample size	Measurement method	Lymphoedema definition	Incidence	Length of follow-up or month of diagnosis	Study quality
Kiel	1996	USA	183	Circumference	>1.5 cm increase from last exam	17.50%	Median follow-up of 20 months	A
McCredie	2001	Australia	809	Self-reported	Self-reported	39%	Median 3.1 years since diagnosis	B
Herd-Smith	2001	Italy	1278	Circumference	>5% differences between arms	15.90%	Median follow-up of 56 months	A
Engel	2003	Germany	990	Unclear	Unclear	38%	60 months after diagnosis	B
Geller	2003	USA	145	Self-reported	Self-reported	38%	6-21 months	B
Powell	2003	USA	727	Arm circumference	>2cm difference between arms	3%	Median follow-up of 72 months	A
Hinrichs	2004	USA	105	Odema	Clinically diagnosed	27%	Unclear	B
Ozaslan	2004	Turkey	240	Circumference	>2cm between arms	28%	Median follow-up of 30 months	A
Deo	2004	India	299	Circumference	>3 cm between arms	33.50%	Minimum 12 months	A
Hayes	2005	Australia	176	Multifrequencybioimpedance	MFBIA: ≥3 SD Self-reported Arm circumferences	0.6-27.8% yes in previous 6 months SOAC: >5 cm or 10%	6 months after diagnosis	A
CLARK	2005	UK	188	Percentage volume	PVD change ≥5%	10%(PVD change≥5%); 20.7%(Any LE at 3 years)	36 months post surgery	A
Armer	2005	USA	100	Arm circumferences	diff-erence(PVD);PVD change ≥2cm	41.2%(<60 years old) 30.6%(≥60 years old)	Unclear	A
Graham	2006	Australia	91	Arm circumferences	Arm circumferences	45%(Arm circumferences) ≥2cmvolume >200ml	Unclear	A
Francis	2006	USA	155	limb volume or circumference	limb volume volume≥5% from pre-operation; circumference≥5% between arms	42%(volume	12 months	A
Ridner	2006	USA	149	Unclear	Unclear	49.66%	Unclear	A
Park	2007	Korea	450	Circumference	≥2cm difference between arms	24.90%	12-24 months	A
Paskett	2007	USA	622	Self-reported	Any swelling in their arm or hand since surgery or in the past 6 months	54%	36 monthd	B
Hayes	2008	Australia	287	Bioimpedance spectroscopy	≥3 SD higher than normative data	33%	6-18 months post surgery	A
McLaughlin	2008	USA	936	Circumferences;self-reported	≥2cm;self-reported	9.19%	Median follow-up of 60 months	A
Shih	2009	USA	1877	Unclear	Unclear	9.60%	Unclear	A
Sagen	2009	Norway	204	limb volume	>200ml or >10% between arms	5%-13%	24 months	A
Meeske	2009	USA	494	Self-reported	Self-reported	24%	Average 50 months after diagnosis	B
Haddad	2010	Iran	355	Circumference	>10% difference between arms	17.50%	48 or more months post surgery	A
Card	2012	USA	1148	Unclear	Unclear	6.80%	59±26.9 months	B
Lee	2012	Korea	96	Circumference	≥2cm difference between arms	60.40%	≥12 months post surgery	A

Table 2. Results of Meta-analysis and Egger's Test and Heterogeneity

Factors	Comparisons	Number of studies	OR	95%CI	P	Egger's test P	Heterogeneity I-squared
Patient-related factors							
BMI(kg/m²)	≥25Kg/m² VS<25Kg/m²	11	1.8	1.3-2.49	p=0.000	0.006	I²=84%
Hypertension	Yes VS No	3	1.83	1.38-2.42	p=0.000	0.329	I²=0.0%
Postoperative complications	Yes VS No	3	2.64	1.10-6.30	p=0.029	0.015	I²=36.7%
Age (years)	≥60 VS<60	12	1.09	0.81-1.48	p=0.566	0.741	I²=65.9%
Marital status	Married vs unmarried	3	1.03	0.56-1.89	p=0.926	0.916	I²=68.7%
Race	African-American VS Caucasian	4	1.01	0.67-1.52	p=0.966	0.726	I²=58.7%
Smoking	Yes VS No	4	1.04	0.83-1.30	p=0.734	0.883	I²=0.0%
Education level	≤high school VS >high school	4	1.2	0.75-1.91	p=0.444	0.18	I²=66.7%
Employment status	Employed VS unemployed	3	1.37	0.86-2.20	p=0.188	0.827	I²=54.5%
Diabetes	Yes VS No	3	0.92	0.49-1.74	p=0.806	0.463	I²=43.4%
Disease-related factors							
Pathologic T classification	T1 VS ≥T2	3	0.57	0.36-0.91	p=0.019	0.428	I²=55.0%
Stage	0&I VS ≥II	5	0.61	0.39-0.93	p=0.023	0.304	I²=29.8%
Lymph node status	Negative VS Positive	3	0.85	0.62-1.18	p=0.340	0.114	I²=0.0%
No. of positive lymph nodes	<1 vs ≥1	4	1.65	0.71-3.85	p=0.244	0.31	I²=90.9%
Treatment-related factors							
Axillary lymph node dissection	Yes VS No	4	3.73	1.16-11.96	p=0.027	0.646	I²=55.3%
Side of treatment	Dominant side --Nondominant side	4	0.83	0.57-1.22	p=0.347	0.651	I²=24.8%
No. of nodes dissected	<20 VS ≥20	5	0.63	0.33-1.20	p=0.163	0.193	I²=87.5%
Breast cancer surgery	Mastectomy VS Breast-conserving	3	1.03	0.57-1.84	p=0.933	0.695	I²=64.3%
Radiotherapy	Yes VS No	15	1.35	1.10-1.66	p=0.005	0.254	I²=63.9%
Chemotherapy	Yes VS No	16	1.38	1.07-1.79	p=0.015	0.409	I²=70.8%
Endocrine therapy	Yes VS No	12	1.11	0.91-1.36	p=0.302	0.442	I²=44.3%
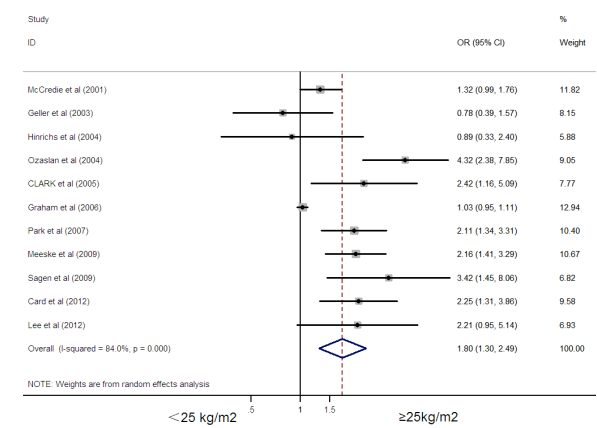
Figure 5. Forest Plot of BMI

Figure 7. Forest Plot of Radiotherapy

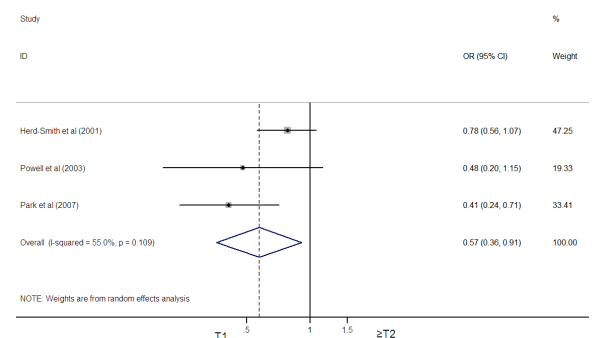**Figure 6. Forest Plot of Chemotherapy**

Figure 8. Forest Plot of Pathologic T Classification

locations of lymphedema in purpose of identifying and decreasing heterogeneity . However, heterogeneity did not decrease (data not shown). Finally, combine and analyze of risk factors using a random effects model. As shown in (Table 2), axillary lymph node dissection (OR=3.73, 95%CI 1.16 to 11.96, p=0.027), postoperative complications (OR=2.64, 95%CI 1.10 to 6.30, p=0.029), hypertension (OR=1.83, 95%CI 1.38 to 2.42, p=0.000), body mass index (OR=1.80, 95%CI 1.30 to 2.49, p=0.000), chemotherapy (OR=1.38, 95%CI 1.07 to 1.79, p=0.015), radiotherapy (OR=1.35, 95%CI 1.10 to 1.66, p=0.005). We found significant protective factors for lymphedema: pathologic T classification (OR=0.57 , 95%CI 0.36 to 0.91, p=0.019), stage (OR=0.60, 95%CI 0.39 to 0.93, p=0.023). Draw forest plots with stata5.0 software respectively (Figure 2-9).
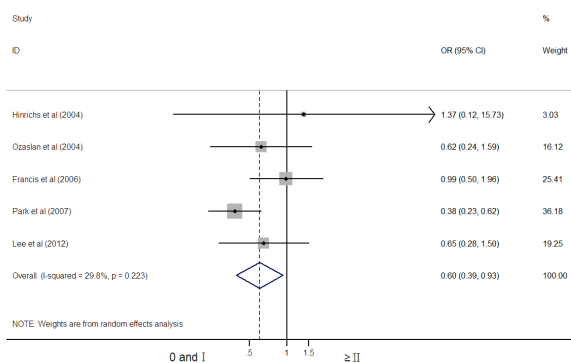
Figure 9. The Forest Plot of Stage

Publication bias and sensitivity analysis using Begg's funnel plot and Egger's test were to estimate the potential publication bias of the included literature.

Discussion

Breast cancer is a common cancer in Asian Pacific Region, with most of patients being treated by surgery and chemo-, radiotherapy. (Kochhar et al., 2013; Gang et al., 2013; Mohammadi et al., 2013; Boonlikit et al., 2013; Cabuk et al., 2014; Hu et al., 2014; Ozkan-Gurdal et al., 2014; El Sharkawi et al., 2014; Meiyanto et al., 2014; Avci et al., 2014; Fouladi et al., 2014; Alipour et al., 2014). We comprehensively reviewed risk factors for lymphedema among breast cancer survivors. The results showed : the risk of group with axillary lymph node dissection (ALND) was 2.72 times compared with group with no ALND. Most studies identified axillary dissection as a risk factor for lymphedema. For example: Paskett et al (Paskett et al., 2007) and Goffman et al (Goffman et al., 2004). Possible Causes: excessive extent of surgery destructed the lymphatic transport between the upper extremity and neck, breast tissue, especially the lymphatic vessel along the cephalic vein. Some studies (Schrenk et al., 2000; Baron et al., 2002) reported there was different risk of lymphedema between sentinel lymph node biopsy (SLND) compared with ALND, and had possibility of reducing the incidence of lymphedema. But this study had few articles which SLND compared with ALND, we can not analyze the incidence of lymphedema between SLND and ALND. Future research should focus on the effect on lymphedema about SLND and different incidences compared with ALND.

In this study, we get an important risk factor of BCRL: postoperative complications and pooled OR and 95%CI (OR=2.64, 95%CI 1.10 to 6.30). *p*=0.029<0.05was considered statistically significant. Postoperative complications mainly referred to infection in this study. McLaughlin et al (Mclaughin et al., 2008) and Hinrichs et al (Hinrichs et al., 2004) also got the same conclusion .But specific reasons were still unclear. Poss-bily, Infection caused by poor wound healing or improper care will further damage lymphatic and hinder the lymphatic reconstruction and establishment of collateral circulation.Thus it will aggravate or cause upper extremity lymphedema.

Kocak (Kocak et al., 2000) and Soran (Soran et al., 2006) think hypertension is risk factors of BCRL. But they did not provide enough evidence to make everyone recognized. Possible reasons: Local lymphatic drainage declined on patients with ALND and could cause upper extremity lymphedema.The study calculated the adjusted OR and 95%CI (OR=1.83, 95%CI 1.38 to 2.42, *p*=0.000) by meta-analysis. So there was significance between hypertension and lymphedema . Breast cancer patients with hypertension increased risk of lymphedema compared with those who not.

Body mass index (BMI) is one of risk factors for lymphedema after breast cancer treatment (Ridner et al., 2011), we also get the same conclusion. Possibly people with larger BMI need greater blood circulation and lymphatic system to facilitate fluid flow. It is likely to cause the apacity of lymph and circulatory imbalanced. Mak et al (Mak et al., 2008) thought the obesity were susceptible to fat necrosis, poor wound healing and infection, thus leading to lymphedema.

Chemotherapy has been used clinically for many years as adjuvant treatment of breast cancer. But whether it can cause lymphedema, many studies have reported mixed results. Paskett (Paskett et al.,2007), Lee (Lee et al.,2012) and Haddad (Haddad et al.) et al thought chemotherapy can cause BCRL.But Tsai (Tsai et al., 2009) reported there was no relation betweeb BCRL and chemotherapy. Patients withchemotherapy were likely to receive invasive surgery and postoperative radiotherapy due to late stage of diseas.We combined OR values and 95%CI among a lot of research: (OR=1.38, 95%CI 1.07 to 1.79, *p*=0.015). So we conclude chemotherapy is one risk factor for BCRL.

Many studies suggest that radiotherapy is an independent risk factor of BCRL (Herd et al., 2011; Engel et al., 2003; Geller et al., 2003; Deo et al., 2004; Ozaslan et al., 2004; Clark et al., 2005; Hayes et al., 2005; Paskett et al., 2007; Hayes et al., 2008; Park et al., 2008; Meeske et al., 2009; Lee et al., 2012). The same conclusion as many studies had been reported. We draw forest plots with stata software: OR=1.35, 95%CI 1.10 to 1.66.Currently reasons radiotherapy-induced of BCRL is not very clear, the reasons were considered that radiotherapy can cause the venous occlusion within radiation field, lymphatic damage and oppress venous and lymphatic due to local muscle fibrosis.

Pathologic T classification and stage were significant protective factors for lymphedema. The lower stage, the lower incidence of lymphedema. On the other hand, the later the stage, the higher degree of malignancy of breast cancer, so the extent of surgery will expand. The risk for lymphedema will become high with it.

Many studies controversied about whether age is a risk factor for lymphedema. Some studies thought young breast cancer survivors were more easier to develop lymphedema (Armer et al., 2005). Young patients may havea higher degree of malignancy of breast cancer. But some persisted patients with old age ones would be easier to develop lymphedema (Kiel et al., 1996). Lymphatic-venous anastomosis will decrease with age older and Lymphatic drainage compensatory capacity also decrease (Clough et al., 2010). We combined many studies with age and did not find obvious correlation between age and lymphedema. In addition, we also combined No. of nodes dissected, No. of positive lymph nodes, Lymph node status

and did not find the relation with lymphedema.

The results of Egger's test showed this study had better stability, publication bias was small, and the data obtained were reliable. So it can provide evidence and guidelines for the prevention and treatment of lymphedema in Clinical work. But limitations of the study: (Cheville et al., 2003) This study only retrieved PubMed, Ovid and other English database and had possibility of missing data, thus affecting research. (Hayes et al., 2012) Potential publication bias of Egger's test was inevitable and impacted the result finally.

In summary, we found that risk factors for BCRL from strong to weak as follows: axillary lymph node dissection, postoperative complications, hypertension, body mass index, chemotherapy, radiotherapy are risk factors for lymphedema after breast cancer treatment. Stage and Pathologic T classification are important protective factors. The results of some studies were inconsistent and different, for example: age, treatment on dominant side and endocrine therapy. Some factors (marital status, race, education level, employment status, smoking) also get more and more attention in recent years. Although in recent years the incidence of BCRL declines, the treatment is still very difficult problem. Lack of effective cure for lymphedema, so preventing its occurrence is particularly important. But risk factors and pathogenesis for BCRL have not been fully elaborated, there need to be confirmed by further studies.

Acknowledgements

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